

Applicant : Stephen Thom et al.
 Serial No. : 10/069,215
 Filed : February 22, 2002
 Page : 2 of 11

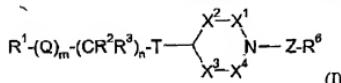
Attorney's Docket No.: 06275-244US1 / A 2214-1P US

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Presently amended) The present invention provides a Δ compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof:



wherein

Z is CR⁴R⁵, C(O) or CR⁴R⁵Z⁺, wherein R⁴ and R⁵ are CH₃;

Z⁺ is C₁₋₄ alkylene, C₂₋₄ alkenylene or C(O)NH;

R¹ represents a C₁₋₁₂ alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ cycloalkyl, C₁₋₆ alkoxy carbonyl and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, phenyl(C₁₋₆ alkyl), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, S(O)₂(C₁₋₆ alkyl), C(O)NH₂, carboxy or C₁₋₆ alkoxy carbonyl); or

R¹ represents C₂₋₆ alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C₁₋₆ alkyl, C₁₋₆ haloalkyl, phenyl(C₁₋₆ alkyl), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, S(O)₂(C₁₋₆ alkyl), C(O)NH₂, carboxy or C₁₋₆ alkoxy carbonyl); or R¹ represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C₁₋₈ alkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ haloalkyl, C₁₋₆ alkoxy(C₁₋₆ alkyl), C₃₋₆ cycloalkyl(C₁₋₆ alkyl), C₁₋₆ alkylthio(C₁₋₆ alkyl),

Applicant : Stephen Thom et al.
 Serial No. : 10/069,215
 Filed : February 22, 2002
 Page : 3 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-IP US

C_1 - C_6 alkylcarbonyloxy(C_1 - C_6 alkyl), C_1 - C_6 alkylS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl), heterocyclyl(C_1 - C_6 alkyl), arylS(O)₂(C_1 - C_6 alkyl), heterocyclylS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl)S(O)₂, heterocyclyl(C_1 - C_6 alkyl)S(O)₂, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, carboxy-substituted C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxylalkoxy, C_1 - C_6 alkylcarboxy-substituted C_1 - C_6 alkoxy, aryloxy, heterocyclyloxy, C_1 - C_6 alkylthio, C_3 - C_7 cycloalkyl(C_1 - C_6 alkylthio), C_3 - C_6 alkynylthio, C_1 - C_6 alkylcarbonylamino, C_1 - C_6 haloalkylcarbonylamino, SO₂H, -NR⁷R⁸, -C(O)NR²³R²⁴, S(O)₂NR¹⁸R¹⁹, S(O)₂R²⁰, ²⁵C(O), carboxyl, C_1 - C_6 alkoxy carbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, phenyl(C_1 - C_6 alkyl), C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, S(O)₂(C_1 - C_6 alkyl), C(O)NH₂, carboxy or C_1 - C_6 alkoxy carbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR⁹, C(O), C(O)NR⁹, NR⁹C(O) or CH=CH; n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R² and R³ independently represents a hydrogen atom or a C_1 - C_4 alkyl group, or (CR²R³)_n represents C_3 - C_7 cycloalkyl optionally substituted by C_1 - C_4 alkyl;

T represents a group NR¹⁰, C(O)NR¹⁰, NR¹¹C(O)NR¹⁰ or C(O)NR¹⁰NR¹¹, wherein R¹⁰ is H; X¹, X², X³ and X⁴ are, independently, CH₂, CHR¹² (wherein each R¹² is, independently, C_1 - C_4 alkyl or C_1 - C_4 cycloalkyl(C_1 - C_4 alkyl)) or C=O; or, when they are CHR¹², the R¹² groups of X¹ and X² or X³ or X⁴ join to form a two- or three-atom chain which is CH₂CH₂, CH₂CH₂CH₂, CH₂OCH₃ or CH₂SCH₃; provided always that at least two of X¹, X², X³ and X⁴ are CH₂;

R⁴ and R⁵ each independently represent a hydrogen atom or a C_1 - C_4 alkyl group;

R⁶ is aryl or heterocyclylphenyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_1 - C_6 alkyl, C_1 - C_6 hydroxylalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy(C_1 - C_6 alkyl), C_3 - C_7 cycloalkyl(C_1 - C_6 alkyl), C_1 - C_6 alkylthio(C_1 - C_6 alkyl), C_1 - C_6 alkylcarbonyloxy(C_1 - C_6 alkyl), C_1 - C_6 alkylS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl), heterocyclyl(C_1 - C_6 alkyl), arylS(O)₂(C_1 - C_6 alkyl), heterocyclylS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl)S(O)₂, heterocyclyl(C_1 - C_6

Applicant : Stephen Thom et al.
Serial No. : 10/069,215
Filed : February 22, 2002
Page : 4 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

alkyl)S(O)₂, C₂-C₆ alkenyl, C₁-C₆ alkoxy, carboxy-substituted C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkoxy, C₁-C₆ alkylcarboxy-substituted C₁-C₆ alkoxy, aryloxy, heterocyclyoxy, C₁-C₆ alkylthio, C₃-C₇ cycloalkyl(C₁-C₆ alkylthio), C₃-C₆ alkynylthio, C₁-C₆ alkylcarbonylamino, C₁-C₆ haloalkylcarbonylamino, SO₂H, -NR¹⁶R¹⁷, -C(O)NR²¹R²², S(O)₂NR¹³R¹⁴, S(O)₂R¹⁵, R²⁶C(O), carboxyl, C₁-C₆ alkoxy carbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, S(O)₂(C₁-C₆ alkyl), C(O)NH₂, carboxy or C₁-C₆ alkoxy carbonyl; R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹⁴, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²² and R²⁴ are, independently hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl(C₁-C₄ alkyl) or phenyl(C₁-C₆ alkyl); and, R¹⁵ and R²⁰ are, independently, C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, C₃-C₆ cycloalkyl, C₃-C₇ cycloalkyl(C₁-C₄ alkyl) or C₁-C₆ alkyl optionally substituted by phenyl; R²⁵ and R²⁶ are, independently, C₁-C₆ alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, S(O)₂(C₁-C₆ alkyl), C(O)NH₂, carboxy or C₁-C₆ alkoxy carbonyl); or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof; provided that when T is C(O)NR²⁴ and R⁷ is optionally substituted phenyl then n is not 0.

2-4. (Cancelled)

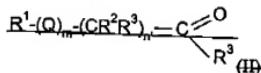
5. (Original) A compound as defined in any one of Examples 1 to 416.

6. (Presently amended) A process for the preparation of a compound of formula (I) as defined in claim 1 which comprises:

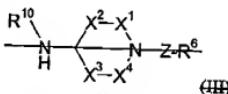
(a) — when n is at least 1, the CR³R⁴ group attached directly to T is CHR⁵ and T is NR¹⁹, reacting a compound of general formula

Applicant : Stephen Thom et al.
 Serial No. : 10/069,215
 Filed : February 22, 2002
 Page : 5 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

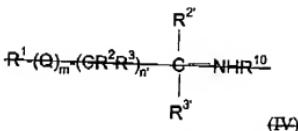


wherein n' is 0 or an integer from 1 to 3 and R^1 , R^2 , R^3 , m and Q are as defined in formula (I), with a compound of general formula

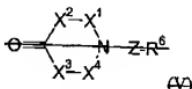


or a salt thereof, wherein X^1 , X^2 , X^3 , X^4 , Z , R^6 and R^{10} are as defined in formula (I), in the presence of a reducing agent; or

(b) when n is at least 1, the CR^2R^3 group attached directly to T is $C(C_1-C_4\text{-alkyl})_2$ and T is NR^{10} , reacting a compound of general formula



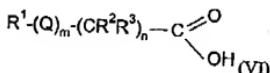
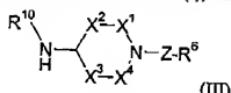
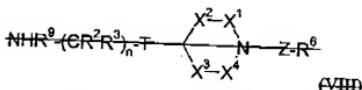
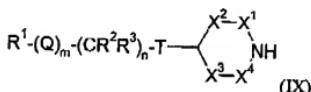
wherein n' is 0 or an integer from 1 to 3, R^2 and R^3 each independently represent a $C_1-C_4\text{-alkyl}$ group, and R^1 , R^2 , R^3 , R^{10} , m and Q are as defined in formula (I), with a compound of general formula



wherein X^1 , X^2 , X^3 , X^4 , Z and R^6 are as defined in formula (I), in the presence of a reducing agent; or

Applicant : Stephen Thom et al.
 Serial No. : 10/069,215
 Filed : February 22, 2002
 Page : 6 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

(ea) when T is $C(O)NR^{10}$, reacting a compound of general formulawherein R^1 , R^2 , R^3 , Q , m and n are as defined in formula (I), with a compound of formula (III)wherein X^1 , X^2 , X^3 , X^4 , Z , R^6 and R^{10} are as defined in formula (I), or a salt thereof as defined in (a) above; or(d) when m is 1 and Q is NR^9 , reacting a compound of general formula (VII), R^1-L^+ , wherein L^+ represents a leaving group (e.g. a halogen atom) and R^1 is as defined in formula (I), with a compound of general formulaor a salt thereof, wherein n , T , X^1 , X^2 , X^3 , X^4 , Z , R^2 , R^3 , R^5 , R^6 and R^9 are as defined in formula (I), or(eb) when at least one of R^4 and R^5 represents a hydrogen atom, reacting a compound of general formula

Applicant : Stephen Thom et al.
 Serial No. : 10/069,215
 Filed : February 22, 2002
 Page : 7 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

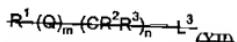
or a salt thereof, wherein R^1 , R^2 , R^3 , Q , m , n , X^1 , X^2 , X^3 , X^4 and T are as defined in formula (I), with a compound of general formula (X), $R^6 - C(O) - R^{20}$, wherein R^{20} represents a hydrogen atom or a C_1 - C_4 alkyl group and R^6 is as defined in formula (I), in the presence of a reducing agent; or

(g) reacting a compound of formula (IX) as defined in (e)(b) above, with a compound of general formula



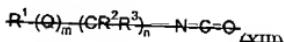
wherein L^2 represents a leaving group (e.g. a halogen atom) and Z and R^6 are as defined in formula (I); or

(g) when T is NR^{10} , reacting a compound of general formula



wherein L^3 represents a leaving group (e.g. a halogen atom) and R^1 , R^2 , R^3 , m , n and Q are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

(h) when T is $NHC(O)NR^{10}$, reacting a compound of general formula

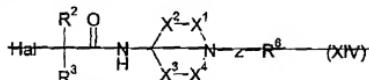


wherein R^1 , R^2 , R^3 , Q , m and n are as defined in formula (I), with a compound of formula (III) or a salt thereof as defined in (a) above; or

Applicant : Stephen Thom et al.
Serial No. : 10/069,215
Filed : February 22, 2002
Page : 8 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

(i) — when T is $\text{C}(\text{O})\text{NH}_2$, Z is CH_2 , n is 1, R² and R³ are hydrogen or C₁-C₄-alkyl and Q is oxygen or sulphur, reacting a compound of formula (XIV).



wherein Hal is a suitable halogen, R^2 , R^3 , R^4 , X^1 , X^2 , X^3 , X^4 , Z , and R^6 are as defined in formula (1) with R^1OH or R^1SH in the presence of a suitable base.

and optionally after (a), (b), or (c), (d), (e), (f), (g), (h) or (i) forming a pharmaceutically acceptable salt or solvate of the compound of formula (I) obtained

7. (Presently amended) A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims claim 1 to 4 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

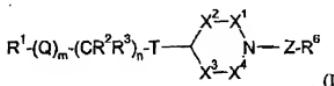
8. (Presently amended) A process for the preparation of a pharmaceutical composition as claimed in claim 7 which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as claimed in any one of claims claim 1 to 4 with a pharmaceutically acceptable adjuvant, diluent or carrier.

9-10. (Cancelled)

11. (Presently Amended) A method of treating ~~an inflammatory disease~~ asthma in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof ~~as defined claim 10.~~

Applicant : Stephen Thom et al.
 Serial No. : 10/069,215
 Filed : February 22, 2002
 Page : 9 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

wherein Z is CR^4R^5 , wherein R^4 and R^5 are CH_2 ;

R^1 represents a 3- to 14-membered saturated or unsaturated ring system which comprises up to two ring carbon atoms that form carbonyl groups and which further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C_1 - C_8 alkyl, C_1 - C_6 hydroxalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy(C_1 - C_6 alkyl), C_3 - C_7 cycloalkyl(C_1 - C_6 alkyl), C_1 - C_6 alkylthio(C_1 - C_6 alkyl), C_1 - C_6 alkylcarbonyloxy(C_1 - C_6 alkyl), C_1 - C_6 alkylS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl), heterocyclic(C_1 - C_6 alkyl), arylS(O)₂(C_1 - C_6 alkyl), heterocyclicS(O)₂(C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl)S(O)₂, heterocyclic(C_1 - C_6 alkyl)S(O)₂, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, carboxy-substituted C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxalkoxy, C_1 - C_6 alkylcarboxy-substituted C_1 - C_6 alkoxy, aryloxy, heterocyclicloxy, C_1 - C_6 alkylthio, C_3 - C_7 cycloalkyl(C_1 - C_6 alkylthio), C_3 - C_6 alkynylthio, C_1 - C_6 alkylcarbonylamino, C_1 - C_6 haloalkylcarbonylamino, SO_2H , $-NR^7R^8$, $-C(O)NR^{23}R^{24}$, $S(O)NR^{10}R^{10}$, $S(O)R^{20}R^{25}C(O)$, carboxyl, C_1 - C_6 alkoxy carbonyl, aryl and heterocyclic;
wherein the foregoing aryl and heterocyclic moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, phenyl(C_1 - C_6 alkyl), C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $S(O)_2$ (C_1 - C_6 alkyl), $C(O)NH_2$, carboxy or C_1 - C_6 alkoxy carbonyl;

 m is 0; n is 2;

each R^2 and R^3 independently represents a hydrogen atom or a C_1 - C_4 alkyl group, or $(CR^2R^3)_n$ represents C_3 - C_7 cycloalkyl optionally substituted by C_1 - C_4 alkyl;

 T represents a group $C(O)NR^{10}$; X^1 , X^2 , X^3 and X^4 are, independently, CH_2 ; R^4 and R^5 each independently represent a hydrogen atom or a C_1 - C_4 alkyl group;

Applicant : Stephen Thom et al.
Serial No. : 10/069,215
Filed : February 22, 2002
Page : 10 of 11

Attorney's Docket No.: 06275-244US1 / A 2214-1P US

R⁵ is phenyl optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C₁-C₈ alkyl, C₁-C₆ hydroxalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy(C₁-C₆ alkyl), C₁-C₇ cycloalkyl(C₁-C₆ alkyl), C₁-C₆ alkylthio(C₁-C₆ alkyl), C₁-C₆ alkylcarboxy(C₁-C₆ alkyl), C₁-C₆ alkylS(O)₂(C₁-C₆ alkyl), aryl(C₁-C₆ alkyl), heterocyclyl(C₁-C₆ alkyl), arylS(O)₂(C₁-C₆ alkyl), heterocyclylS(O)₂(C₁-C₆ alkyl), aryl(C₁-C₆ alkyl)S(O)₂, heterocyclyl(C₁-C₆ alkyl)S(O)₂, C₂-C₆ alkenyl, C₁-C₆ alkoxy, carboxy-substituted C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ hydroxalkoxy, C₁-C₆ alkylcarboxy-substituted C₁-C₆ alkoxy, aryloxy, heterocycloloxy, C₁-C₆ alkylthio, C₁-C₇ cycloalkyl(C₁-C₆ alkylthio), C₂-C₆ alkynylthio, C₁-C₆ alkylcarboxylamino, C₁-C₆ haloalkylcarboxylamino, SO₂H, -NR¹⁶R¹⁷, -C(O)NR²¹R²², S(O)₂NR¹³R¹⁴, S(O)₂R¹⁵, R²⁶C(O), carboxyl, C₁-C₆ alkoxy carbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of: halogen, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, S(O)₂(C₁-C₆ alkyl), C(O)NH₂, carboxy or C₁-C₆ alkoxy carbonyl;
R⁷, R⁸, R⁹, R¹⁰, R¹¹, R¹³, R¹⁴, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²¹, R²², R²³ and R²⁴ are, independently, hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ hydroxalkyl, C₃-C₇ cycloalkyl, C₃-C₇ cycloalkyl(C₁-C₄ alkyl) or phenyl(C₁-C₆ alkyl); and,
R¹⁵ and R²⁰ are, independently, C₁-C₆ alkyl, C₁-C₆ hydroxalkyl, C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl(C₁-C₄ alkyl) or C₁-C₆ alkyl optionally substituted by phenyl;
R²⁵ and R²⁶ are, independently, C₁-C₆ alkyl or phenyl (optionally substituted by one or more of: halogen, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, S(O)₂(C₁-C₆ alkyl), C(O)NH₂, carboxy or C₁-C₆ alkoxy carbonyl).